REMARKS

Claims 31-36, 43-45, 51, and 55-60 are pending in the application and under examination. Claims 31, 32, and 60 are objected to for informalities. Claims 31-36, 43-45, 51, and 55-60 stand provisionally rejected for double patenting. Claims 31-36, 43-45, 51, and 55-60 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement and under 35 U.S.C. § 112, second paragraph for indefiniteness.

Applicants note that the previous rejection of claims 31-36, 43-45, 51, and 55 under 35 U.S.C. § 103(a) over Quarto *et al.* (1997) in view of Binette *et al.* (1998) and Kolettas *et al.* (1995) has been withdrawn.

The specification is objected to for informalities.

Each of the issues raised in the Final Office Action is addressed below.

Amendments

Claims 31, 32 and all claims dependent therefrom were amended to include the limitation to "chondrocyte cells." Support for this amendment is found throughout the specification, for example, on page 14 (line 32) through page 15 (line 30).

Claim 31 was amended to remove mention of a "marker co-detectable with these markers" and of the method steps a) through f) to identify a co-detectable marker.

Claim 32 was amended to remove mention of "marker co-detectable with said ALK-1 marker" and of the method steps a) through f) to identify said co-detectable marker. Additionally, a full stop was added after "phenotypic stability."

Claim 33 was amended to remove mention of "marker co-detectable with these markers." Additionally, a colon was added after "comprising," an erroneous full stop was removed at the end of step a), and a semi-colon and the word "and" were added after "FGFR-3."

Claim 55 was amended to remove mention of markers co-detectable with the negative marker ALK-1, to add a colon after "comprising," and to correct an obvious

error in the drafting of the claim. Indeed, claim 55 refers to the method of claim 32, which recites the identification of cells having phenotypic stability based on the absence of expression of the ALK-1 marker. Claim 55, as previously examined, included in its step a) the hybridisation to probes specific for the negative marker ALK-1 and in its step b) the identification of "cells which hybridize with said probe of said positive marker for chondrocyte phenotypic stability" (emphasis added).

Applicants respectfully submit that it is clear that what was meant was that, as ALK-1 is demonstrated in the present application to be a negative marker for chondrocyte phenotypic stability, the cells having chondrocyte phenotypic stability are the cells not expressing the negative ALK-1 marker and therefore, the cells not hybridizing to the probes corresponding to the negative marker ALK-1.

Moreover, claim 55 was amended to remove an erroneous full stop in step a). Additionally, a semi-colon and the word "and" were added after "ALK-1."

Claim 60 was amended to remove the duplicate mention of the expression "further comprising."

Newly introduced claim 61 reads on a method of identifying cells having chondrocyte phenotypic stability as cells co-expressing the positive markers FGFR-3 and type II collagen. Support for this new claim is found in the specification, for example, in Example 9.

No new matter has been added by the present amendments.

Applicants note that these amendments were made solely to advance prosecution, and reserve the right to prosecute any cancelled subject matter in this or a continuing application.

Specification

Applicants, as requested, have amended the specification on page 20 to reference the amino acid sequence for FGFR-3.

Claim objections

Claims 31, 32, and 60 have been objected to on various grounds. In view of the present amendments to each of these claims, these objections should be withdrawn.

Double Patenting

Claims 31-36, 43-45, 51, and 55-60 stand provisionally rejected on the ground of non-statutory double patenting over claims 3-15, 27, 30, and 33 of co-pending application No. 10/422,475. Applicants, as noted previously, will address this issue, if appropriate, upon an indication of allowable subject matter.

Rejections under 35 U.S.C. § 112, first paragraph—Enablement

Claims 31-36, 43-45, 51, and 55-60

Claims 31-36, 43-45, 51, and 55-60 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. More particularly, the Examiner states "the specification, while being enabling for type 2 collagen as a marker which is co-expressed with FGFR-3, does not reasonably provide enablement for any other markers which may be co-expressed with all positive markers" (*see*, Final Office Action, page 5, last paragraph).

Without acquiescence to the Examiner's assertion, amended claim 31, and claims dependent therefrom, solely refer to the BMP-2 and/or FGFR-3 positive markers and no longer refer to markers co-expressed therewith.

Applicants respectfully submit that amended claim 31, and claims dependent therefrom, are thus enabled and request that the § 112 rejection be withdrawn.

Claim 32

Claim 32 was rejected for also failing to comply with the enablement requirement. More specifically, the Examiner states "the specification does not provide any markers which could be considered as "co-expressed with" the negative markers ALK-1 and collagen type X" (*see*, Final Office Action, page 6, second paragraph).

Without acquiescence to this assertion, claim 32, as amended, solely refers to the ALK-1 negative marker and not to markers co-expressed therewith. As the Examiner has not questioned the enablement of the ALK-1 marker, Applicants respectfully request that the § 112 rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph—Indefiniteness

Claims 31-36, 43-45, 51, and 55-60 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In view of the present amendments to the claims, Applicants submit that the rejection of claims 31-36, 43-45, 51, and 55-60 is rendered moot and request the withdrawal of this rejection.

On an additional issue, Applicants address the Examiner's treatment of Yayon et al (WO 96/41620 – Yeda Research and Development Co.) as follows. Here the Examiner indicates that "(i)t would appear from the teachings of Yayon et al (WO 96/41620 – Yeda Research and Development Co.) that the marker FGFR-3 (a positive marker, as taught in the instant specification) is indicative of mesenchymal skeletal progenitor cells, which can differentiate into bone and/or cartilage, and therefore, that FGFR-3 would be insufficient as a positive marker by itself to indicate cells having chondrocyte phenotypic stability" (*see*, Final Office Action, page 8, first paragraph). Applicants respectfully disagree.

Yayon et al. (WO 96/41620) disclose a method of identifying mesenchymal

skeletal progenitor cells using FGFR-3 as a marker based on the identification of FGFR-3 positive cells in the perichondrium of bones.

Applicants note that the identification by Yayon et al. of FGFR-3 as a marker for mesenchymal skeletal progenitor cells is questionable. Indeed, the term mesenchymal skeletal progenitor cells is indicated in Yayon et al. to encompass a broad range of cells including (a) mesenchymal stem cells which are able to differentiate into skeletal progenitor cells, (b) skeletal progenitor cells, (c) precartilagenous stem cells, and (d) preosteogenic stem cells or a combination of two or more of the above cell types (see page 3, last paragraph).

Other publications have demonstrated that at least a subpopulation of skeletal precursor cells obtainable from periosteum, bone marrow, and synovial membrane are FGFR-3 negative, see e.g. WO 01/25402 (copy enclosed). In addition, Applicants submit that the data presented in Yayon et al. are in contrast with the observations by Sasse et al. (3rd conference of the International Cartilage Repair Society, April 27-29, 2000, Abstract 25, Poster Session Basic Science A; copy enclosed). This abstract reports the results on chondrocytes from bovine fetal, newborn, and adult articular cartilage. All three cell types showed abundant expression of FGFR-3 in primary chondrocytes. FGFR-3 is lost on dedifferentiation. In addition, bone marrow mesenchymal cells differentiating to bone or cartilage showed an increase of FGFR-3 expression only after differentiation. Accordingly, Sasse et al. report that dedifferentiation is associated with loss of FGFR-3 expression. The reason for the discrepency between the data obtained by Sasse et al. and those provided in Example 3 of Yayon et al. may be due to the fact that Yayon et al. analyzed embryonic tissue (Page 10, chondrocyte culture). It is well known that nature sometimes re-uses the biochemical machinery of embryogenesis for different functions in the post-natal animal. This is particularly true for growth factors. Accordingly, the identification of FGFR-3 bearing (or non-bearing) cells in the embryo is not a reliable indicator of the function of a marker in the same cells post-natally. Accordingly, it is

submitted that the alleged expression data presented in Yayon et al. are irrelevant to the interpretation of Applicants' specification.

Despite the fact that Applicants consider the teaching by Yayon et al. to be misleading and irrelevant, Applicants further emphasize that the claimed invention is not incompatible with an alleged expression of FGFR-3 on cell types other than chondrocytes. Indeed, it is clear that FGFR-3 is not solely expressed on chondrocytes but is expressed by different cell types. The inventors have however found that in chondrocytes, FGFR-3 is not constitutively expressed, but its expression is linked to the ability of the chondrocyte cells to produce stable hyaline cartilage. Accordingly, the claimed methods specify that the chondrocyte phenotypic stability of a chondrocyte cell population can be assessed based on whether or not FGFR-3 is expressed. That FGFR-3 expression correlates with the ability of a chondrocyte cell population to produce stable hyaline cartilage is demonstrated in the Examples.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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